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b) ~~transfecting/transducing~~ transfected *in vitro* a population of ~~chondrocyte cells~~ chondrocytes with said recombinant vector, resulting in a population of ~~transfecting/transducing~~ transfected connective tissue cells; and

c) injecting a composition comprising the ~~transfecting/transducing~~ transfected population of chondrocyte cells chondrocytes and a pharmaceutically acceptable carrier without scaffolding into a joint space of a mammal such that expression of the DNA sequence encoding TGF β 1 or BMP within the joint space occurs resulting in the generation of hyaline cartilage in the joint space.

14. (Previously presented) The method of claim 13, wherein said transfection is accomplished by liposome encapsulation, calcium phosphate coprecipitation, electroporation and DEAE-dextran mediation.

15. (Original) The method of claim 3, wherein said plasmid is pmTB1.

16.-22. (Canceled)

REMARKS

Claims 1-5 and 13-15 are pending in the application. No new matter has been inserted into the application. The amendments to the claims have been made merely to further clarify the presently claimed invention. Accordingly, entry of the amendments to the application is respectfully requested.

Claim Objections

The Examiner indicates that claim 15 recites "and" and that this word should be replaced with the word "or". However, the word "and" does not appear in claim 15.

Rejection Under 35 U.S.C. 112, first paragraph

Claims 1-5 and 13-15 have been rejected under 35 U.S.C. 112, first paragraph because the application allegedly contains new matter, and that the specification allegedly

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does not provide enabling disclosure for treating arthritis, using any protein of the TGF superfamily, any connective tissue cells or regenerating any connective tissue. Applicants traverse this rejection. Reconsideration and withdrawal thereof are respectfully requested.

The presently claimed invention is directed to a method of regenerating hyaline cartilage, comprising:

- a) generating a recombinant viral or plasmid vector comprising a DNA sequence encoding transforming growth factor $\beta 1$ (TGF- $\beta 1$) or BMP operatively linked to a promoter;
- b) transfecting *in vitro* a population of chondrocytes with said recombinant vector, resulting in a population of transfected connective tissue cells; and
- c) injecting a composition comprising the transfected population of chondrocytes and a pharmaceutically acceptable carrier without scaffolding into a joint space of a mammal such that expression of the DNA sequence encoding TGF $\beta 1$ or BMP within the joint space occurs resulting in the generation of hyaline cartilage in the joint space.

The present application is also directed to a method of treating osteoarthritis comprising:

- a) generating a recombinant viral or plasmid vector comprising a DNA sequence encoding transforming growth factor $\beta 1$ or BMP operatively linked to a promoter;
- b) transfecting *in vitro* a population of chondrocytes with said recombinant vector, resulting in a population of transfected chondrocytes; and
- c) transplanting said transfected chondrocytes without scaffolding by intraarticular injection to an osteoarthritic joint space of a mammalian host, such that expression of said DNA sequence within said joint space results in regenerating connective tissue.

In the presently claimed invention, chondrocytes are transfected or transduced with TGF $\beta 1$ or BMP and the resultant composition along with a pharmaceutical carrier which

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does not include scaffolding or any other such physical matrix is injected into the joint space to regenerate hyaline cartilage. Using chondrocytes is disclosed at least at pages 5 and 9 in the present application. Use of BMP protein is discussed at least at page 5 in the present specification.

To further indicate support for "treating osteoarthritis with chondrocyte transfected with TGF- β 1 or BMP", the Examiner's attention is directed to page 1 in the specification of the present application where the following passage is found:

"In the orthopedic field, degenerative arthritis or osteoarthritis is the most frequently encountered disease associated with cartilage damage. Almost every joint in the body, such as the knee, the hip, the shoulder, and even the wrist, is affected. The pathogenesis of this disease is the degeneration of hyaline articular cartilage (Mankin et al., J Bone Joint Surg, 52A: 460-466, 1982). The hyaline cartilage of the joint becomes deformed, fibrillated, and eventually excavated. If the degenerated cartilage could somehow be regenerated, most patients would be able to enjoy their lives without debilitating pain."

Since the present application discloses that hyaline cartilage is made using chondrocyte transfected with TGF- β 1 or BMP, it is within the purview of the present invention that osteoarthritis is also treated by injecting to a patient suffering from osteoarthritis a substance that generates hyaline cartilage.

Applicants respectfully submit that given the guidance presented in the instant specification, a person of ordinary skill in the art would know how to transfect or transduce chondrocyte with genes encoding TGF β 1 or BMP and inject them into the knee joint. These are discussed in detail in which fibroblast/TGF β 1 has been specifically and without limitation exemplified. However, the application explicitly allows for the use of chondrocytes to regenerate cartilage following the same or similar method as using fibroblasts applying well-

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known molecular biological techniques. Thus, applicants submit that the present application provides a fully enabling description of the presently claimed invention.

Applicants respectfully submit that given the guidance presented in the instant specification, the application provides an enabling disclosure for treating osteoarthritis especially considering the regeneration of hyaline cartilage in rabbits as exemplified in the present application. Regeneration of hyaline cartilage can be thought of as *de facto* treating osteoarthritis because osteoarthritis is caused by the mechanical wearing away of the cartilage, and thus regeneration of cartilage replenishes the degraded cartilage to treat osteoarthritis. Furthermore, no immuno-rejection is seen by the inventive procedure. Thus, applicants submit that the present application provides a fully enabling description of the presently claimed invention. Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. 112, second paragraph

Claims 1-5 and 13-15 have been rejected as being indefinite. The claims have been amended in order to remove the objected to language. Thus, this rejection has been overcome.

Obviousness-Type Double Patenting

Claims 1-5 and 13-15 have been provisionally rejected under the judicially created doctrine of obviousness type double patenting over claims 1-11 of U.S. Patent No. 6,797,703, application number 09/702,718. Applicants traverse this rejection. Reconsideration and withdrawal of this rejection are respectfully requested. Applicants note that since the priority dates of the instant application and U.S. Patent No. 6,797,703 are the same, it is believed that any patent issuing from the instant application and U.S. Patent No. 6,797,703 would expire on the same date. Therefore, it is believed that this rejection is moot.

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Rejection Under 35 U.S.C. 103(a) Over Naughton '477 in view of Ikeda (Ikeda et al., Sept. 1998, J. Rheumatol., Vol. 25, pages 1666-1673) and van Beuningen (van Beuningen et al., Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pages 306-317)

Claims 1-5 have been rejected under 35 U.S.C. 103(a) as being obvious over Naughton '477 in view of Ikeda and van Beuningen. Applicants traverse this rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants note that claim 1 recites that the chondrocytes are without scaffolding. Therefore, as the Examiner has noted, the presently claimed invention is free of prior art.

Conclusion

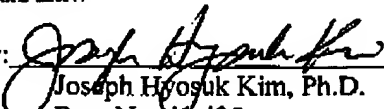
It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. 502486 for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a credit card payment enclosed herewith and to credit any overpayment to said Deposit Account No. 502486.

Respectfully submitted,

JHK Law

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